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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BIOGEN IDEC / FINNEGAN HENDERSON, LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,961	AMBROSE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *46 and 47* is/are withdrawn from consideration.

5)☒ Claim(s) *21* is/are allowed.

6)☒ Claim(s) *6-8,12-18,20 and 22-45* is/are rejected.

7)☒ Claim(s) *1-5,9-11, 19* is/are objected to.

8)☒ Claim(s) *1-47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-45, drawn to a non-naturally occurring BAFF-R glycoprotein, nucleic acid encoding the same, and methods of use in the reply filed on 24 July 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 46-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 24 July 2008.

Claims 1-45 are under consideration in the instant application.

Claim Objections

1. Claims 1-16, 19, 24-35, 39-40, 42-45 are objected to because of the following informalities:

2. Claims 1-16, 19, 24-34, 39-40, 44-45 use the acronym "BAFF-R" and "BAFF" without first defining what they represent in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

3. In claim 13, line 2, the phrase "as set out" should be deleted. Also, at the end of line 3, the term "and" should be deleted.

4. In claim 14, lines 1 and 2, the term "an" should be amended to recite "the" since there can only one amino acid at that particular position.

5. In claim 15, lines 1 and 2, the term "an" should be amended to recite "the" since there can only one amino acid at that particular position.

6. In claim 16, line 4, the phrase "amino acid" should be amended to recite "amino acids".

7. In claim 31, line 2, the phrase "amino acids substitutions" should be amended to recite "amino acid substitutions".

8. In claim 35, parts (a)-(f), the word "from" should be deleted.

9. Applicant is advised that should claim 42 be found allowable, claim 43 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6-8, 25-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 6-8 recite the limitation "...glycoprotein of claim 5, wherein the deletion..." in line 1. There is insufficient antecedent basis for this limitation in the claims. It is noted that claim 5 does not recite a deletion, rather claim 1.

12. Claims 44-45 are indefinite because they recite the phrase "...having an apparent affinity..." in line 1. It is not clear if the glycoprotein has an affinity for BAFF or not. (Please note that this issue could be overcome by amending the claims to recite, for example, "...having an affinity...".)

13. Claims 25-45 are indefinite because claim 25, line 1 recites the phrase "...substantially as set out from amino acid 13 to amino acid 43...". It is not clear what amino acid sequence this limitation encompasses. The metes and bounds of the claims cannot be determined by one skilled in the art.

14. Claims 12-18, 20, 22-24, 32, 35, 37-38 are indefinite because the elements recited in claims 12, 20, 32, and 35 do not constitute proper Markush groups. See MPEP § 2173.05(h). (Please note that this issue could be overcome by amending claim 12, line 2 to recite for example, "...polypeptide having an amino acid sequence selected from the group comprising...".)

15. Claims 29-31 are indefinite because it is not clear what amino acid sequence these claims are referring to. For instance, claims 29-31 depend from claim 25 which recites a first polypeptide sequence and a second polypeptide sequence. However, claims 29-31 do not indicate which they are referring to. (Please note that this issue could be overcome by amending the claims to recite, for example, "...The BAFF-R fusion polypeptide of claim 25, wherein the first polypeptide comprises...".)

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 23-32, 34, 37-38, 40-43, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a BAFF-R fusion protein comprising a first polypeptide comprising the amino acid sequence from amino acid 13 (or 14) to amino acid 43 of SEQ ID NO: 1, *does not reasonably provide enablement* for a BAFF-R fusion polypeptide comprising a first polypeptide comprising an amino acid sequence substantially as set out from amino acid 13 (or 14) to amino acid 43 of SEQ ID NO: 1. Also, the specification while being enabling for an isolated host cell, a composition comprising the nucleic acid encoding the BAFF-R glycoprotein, and a method for treating an autoimmune disorder characterized by an elevated BAFF level comprising administering the claimed polypeptides *does not reasonably provide enablement* for a host cell, a pharmaceutical composition comprising the nucleic acid encoding the BAFF-R glycoprotein, and a method for treating an immunological disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 23 is directed to a host cell comprising a nucleic acid. Claim 25 is directed to a BAFF-R fusion polypeptide comprising (a) a first polypeptide comprising an amino acid sequence substantially as set out from amino acid 13 to amino acid 43 or amino acids 14 to 43 of SEQ ID NO: 1 fused to (b) a second amino acid sequence comprising at least a portion of an immunoglobulin constant region, and optionally (c) a linker joining the first and the second sequences, wherein the BAFF-R fusion polypeptide does not include amino acid 50 to amino acid 56 of SEQ ID NO: 1. Claim 28 recites that the first polypeptide of the fusion polypeptide

comprises an amino acid sequence from amino acid 8 to amino acid 49 of SEQ ID NO: 1. Claim 29 recites that the fusion polypeptide comprises an amino acid sequence substantially identical to SEQ ID NO: 1 from amino acid 13 to amino acid 43. Claim 30 recites that the fusion polypeptide comprises an amino acid sequence substantially identical to SEQ ID NO: 1 from amino acid 14 to amino acid 43. Claim 32 recites that the first polypeptide of the BAFF-R fusion polypeptide comprises various amino acid fragments. Claim 34 recites a nucleic acid encoding a BAFF-R fusion polypeptide. Claims 40-41 recite a pharmaceutical composition. Claims 42 and 43 recite a method for treating an immunological disorder comprising administering a therapeutically effective amount of a BAFF-R fusion polypeptide or nucleic acid to a patient in need of treatment, thereby treating the immunological disorder.

(i) The specification of the instant application teaches the term "BAFF-R" refers to mutant or wild-type human BAFF receptor and variants thereof (page 12, [0045]). Claims 25-32, 34, 37-38, 40, 42-43, and 45 recite the phrase "...an amino acid sequence..." and thus, are broadly interpreted by the Examiner as reading upon: (i) first polypeptide variants with any number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NO: 1 (smaller than amino acids 13 to 43, amino acids 14 to 43, and amino acids 14 to 49), including sequences only 2 amino acids in length. However, the specification does not teach any variant, fragment, or derivative of the BAFF-R fusion polypeptide other than the moieties listed in Table 1 at page 31. The specification clearly teaches that residues P44-A49 of the first polypeptide of the BAFF-R fusion are required for proper ligand binding (page 30). The specification also teaches that the N-terminal deletion hBAFF-R(A14-A72):Fc retains BAFF binding ability while hBAFF-R(C20-A72):Fc does not. It is also noted that the BAFF-R fusion polypeptide of claims 25-32, 34, 37-

38, 40, 42-43, and 45 does not have any particular activity limitations. Thus, undue experimentation would be required of the skilled artisan to generate the large number of BAFF-R fusion polypeptide derivatives recited in the claims.

Additionally, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. As demonstrated by the instant specification, certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

(ii) The Examiner has interpreted claims 23, 24, and 38 as reading upon isolated host cells, as well as host cells in the context of host cells intended for gene therapy. Claims 41-43 (a pharmaceutical composition and methods of administration) have also been interpreted by the Examiner as reading upon treatment of a disease in an animal with a BAFF-R nucleic acid molecule. The specification of the instant application teaches that diseases and disorders that are characterized by increased levels or biological activity of BAFF may be treated with therapeutics that antagonize BAFF or BAFF-R activity and include administering to subject a nucleic acid

encoding ΔBAFF-R or a ΔBAFF polypeptide (page 24, lines 2-6). However, the specification does not teach any methods or working examples that indicate a ΔBAFF-R nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the ΔBAFF-R nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a ΔBAFF-R nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a ΔBAFF-R nucleic acid in the cell of an organism or be able to produce a ΔBAFF-R protein in that cell. (Please note that this issue could be overcome *in part* by amending claims 23, 24, and 38 to recite, for example, "An isolated host cell…").

(iii) Regarding claims 42-43, the specification teaches that the term "immunological disorder" refers to disorders and conditions in which an immune response is aberrant (page 14, [0050]). Thus, the phrase "immunological disease" in the claims is interpreted by the Examiner to be broad, in that it encompasses any and all immunological diseases or disorders. The specification lists examples of disorders that can be treated, such as rheumatoid arthritis, asthma, psoriasis, diabetes, multiple sclerosis, B cell cancers, demylinating disorders, indirect T cell immune response, etc. (page 14, [0050]). However, the state of the art at the time the instant invention was made teaches that BAFF-R is a target for autoimmune disorders that that have an elevated BAFF level, such as systemic lupus erythematosus and rheumatoid arthritis (see for example, Kalled et la. Expert Opin Ther Targets 7(1): 115-123, 2003; see page 115; page 117-120;; Tange et al. Seminars Immunol 18: 305-317, 2006; page 310-311). Undue experimentation would be required of the skilled artisan to administer the BAFF-R glycoprotein and nucleic acid to individuals with all possible immunological disorders and diseases and treat the disorder or disease. One skilled in the art would also not be able to predict from the relevant references cited above and the *in vivo* B cell experiment of the instant specification (Example 8, pages 40-42) that the BAFF-R glycoprotein and nucleic acid would be able to treat all possible immunological disorders.

Due to the large quantity of experimentation necessary to (1) generate the large number of derivatives recited in the claims, (2) to introduce and express a ΔBAFF-R nucleic acid in a cell of an organism for therapy, and (3) treat all possible immunological disorders; the lack of direction/guidance presented in the specification regarding how to introduce a ΔBAFF-R nucleic acid in the cell of an organism to be able produce that ΔBAFF-R, the absence of working

examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any functional limitations, any cell type limitations, or any specific diseases, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Schneider et al. Immunol Lett 88: 57-62, 2003 (review of BAFF and its involvement in the regulation of B cell survival)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
24 October 2008

/Bridget E Bunner/
Primary Examiner, Art Unit 1647